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New Perspectives on the Treatment of Metastatic Renal Cell Carcinoma: An Introduction and Historical Overview

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In 2010, kidney or renal pelvis cancers are expected to be diagnosed in an estimated 58,240 individuals and to be responsible for 13,040 deaths in the U.S. [1]. Renal cell carcinoma (RCC) arises from the renal epithelium and represents approximately 85% of all kidney cancers [2]. Initial treatment for localized RCC is surgery, but 20%–30% of patients typically relapse, with a median time to relapse of 1–2 years [3]. In addition, approximately one third of patients with RCC present with metastatic disease [4]. Until recently, patients with RCC whose disease had metastasized had few treatment options. Cytokines (interleukin-2 and interferon-α) were the standard therapy but were associated with relatively low response rates and significant toxicity [5–7].

The treatment of metastatic RCC has changed dramatically in the past 5 years with the availability of new treatment options (Fig. 1). Molecular research into the pathogenesis of RCC has provided valuable information on the signaling pathways known to be altered in RCC, including vascular endothelial growth factor (VEGF) and its receptor (VEGFR) and the mammalian target of rapamycin (mTOR), a key kinase regulating cell growth and proliferation, cellular metabolism, and angiogenesis. Molecularly targeted therapies were developed specifically to target these signal transduction pathways. These include bevacizumab, a monoclonal antibody targeting VEGF; the tyrosine kinase inhibitors sunitinib, sorafenib, and pazopanib, which target VEGFR and other receptor tyrosine kinases; and everolimus and temsirolimus, selective mTOR inhibitors. In pivotal phase III trials, bevacizumab, sunitinib, sorafenib, pazopanib, and temsirolimus have shown clinical benefit for patients with treatment-naïve or cytokine-pretreated RCC by prolonging progression-free or overall survival (temsirolimus only) times [8–15]. Clinical benefit was observed in patients with metastatic RCC treated with everolimus as a second-line therapy after failure of sunitinib or sorafenib, as demonstrated by the more than double median progression-free survival time, compared with placebo [16, 17].

Because of their distinct molecular targets, the safety profiles of these agents are drug class–specific. The majority of adverse events observed in phase III trials of these agents were grade 1 or 2, although grade 3 or 4 toxicities were observed in 10%–20% of patients [18]. Consequently,

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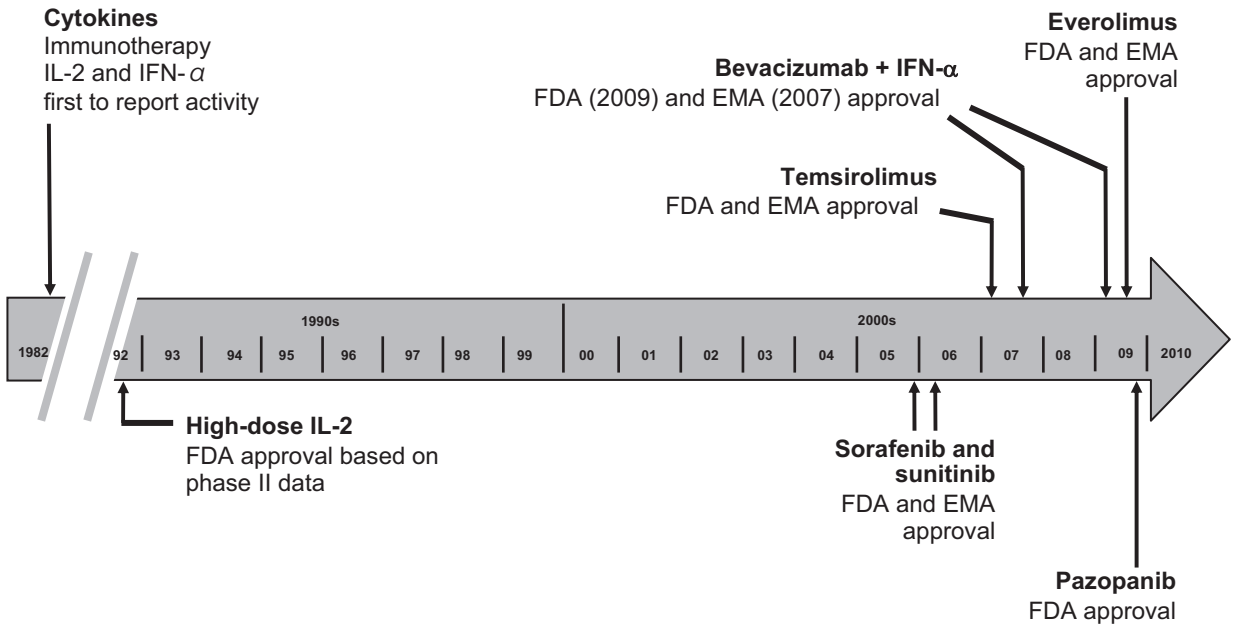

Figure 1. Timeline of treatments for renal cell carcinoma.
Abbreviations: EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; IFN, interferon; IL, interleukin.

patients treated with targeted therapies require close monitoring with specific management algorithms developed to optimize patient benefit. Given the generally poor prognosis of patients with metastatic RCC and the toxicity associated with therapy, health-related quality of life and patient-reported outcomes have become an important consideration in this patient population because survival for these patients is prolonged [19].

The efficacy and safety profiles of these targeted agents have resulted in U.S. and European regulatory approvals and updated recommendations within the U.S. (National Comprehensive Cancer Network) and European (European Organisation for Research and Treatment of Cancer, European Society of Medical Oncology, European Association of Urology) clinical practice guidelines, thus revolutionizing the treatment of patients with metastatic RCC [3, 20–22]. Given the availability of multiple new targeted agents within a short period of time, the optimal sequence and/or combination of therapies for patients with RCC is an increasingly active area of research. Ongoing clinical trials currently are investigating combination and sequential therapy with these targeted agents to identify regimens that will benefit patients with advanced RCC.

In this supplement, we review the pathogenesis and diagnosis of RCC and the efficacy and safety of currently available targeted therapies, including recommendations for adverse event management. We also discuss quality of life considerations when selecting targeted therapies for RCC and current treatment guidelines based on evidence-based medicine. In addition, preliminary data comparing the cost-effectiveness of these therapies in the first- and second-line settings are discussed. Finally, we highlight future directions including trials to determine the optimal setting and sequence of these agents and those that investigate novel agents, combinations, or sequential therapies to improve patients' survival outcomes.

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